IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

MANTZARIDIS et al

Serial No. 09/973,568

Filed: October 9, 2001

For: ANAESTHESIA CONTROL SYSTEMS

Atty. Ref.: 2425-18

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Examiner: J.M. Foreman

* * * * * * * * * * * *

March 26, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SUBMISSION OF PRIORITY DOCUMENTS

It is respectfully requested that this application be given the benefit of the foreign filing date under the provisions of 35 U.S.C. §119 of the following, a certified copy of which is submitted herewith:

Application No.	Country of Origin	Filed
9618998.0	United Kingdom	September 11, 1996

Respectfully submitted,

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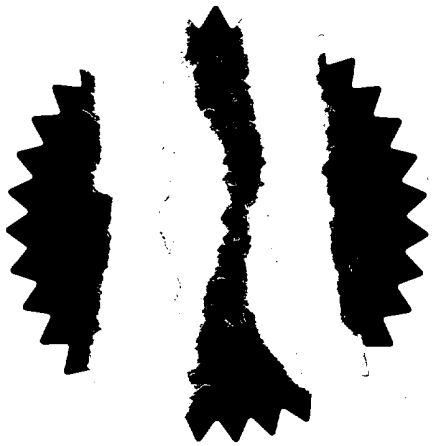

Signed R. Mahoney

Dated 5 March 2004

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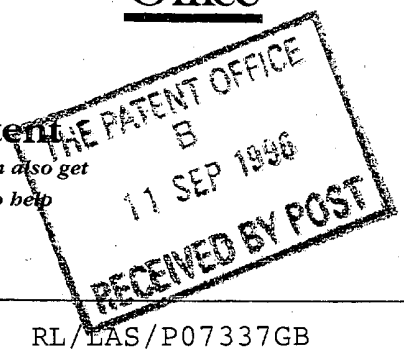

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1. Your reference

RL/LAS/P07337GB

2. Patent application number
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9618998.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

The University Court of The University of Glasgow

No. 2 The Square
University Avenue
Glasgow
G12 8QQ

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

79264001

4. Title of the invention

Anaesthesia Control

5. Name of your agent *(if you have one)*

Cruikshank & Fairweather

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

19 Royal Exchange Square
Glasgow
G1 3AE
United Kingdom

Patents ADP number *(if you know it)*

54002

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Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

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a) any applicant named in part 3 is not an inventor, or
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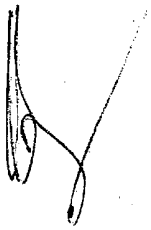

Continuation sheets of this form

Description 16

Claim(s)

Abstract

Drawing(s) 4

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Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

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11. I/We request the grant of a patent on the basis of this application.

Signature Cruikshank & Fairweather Date 10.09.96

CRUIKSHANK & FAIRWEATHER

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Robert Lind - Tel: 0141 221 5767

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ANAESTHESIA CONTROL

The present invention relates to anaesthesia control and in particular to a system and method for calculating an index representative of the depth of anaesthestic. The invention is applicable in particular, though not necessarily, to a system and method for providing closed-loop anaesthesia control such as will safely maintain a patient in an unconscious state without requiring human intervention.

Conventional anaesthesia systems require an anaesthetist to manually control the anaesthetic dose given to a patient in dependence upon displayed vital signs, e.g. heart rate and blood pressure, and upon the visually observable reaction of the patient. However, when a patent is paralysed and ventilated these vital signs are not completely reliable as indicators of anaesthesia depth and there have been reports of patients being awake during an operation despite their vital signs being within normal limits.

In an attempt to eliminate or reduce the possibility for error in the application of an anaesthetic, research has been carried out into providing a more reliable indication of anaesthesia depth and in particular a more direct index of anaesthesia depth. Almost all proposals have relied upon the analysis of cerebral electrical activity and more particularly of recorded electroencephalographic (EEG) signals.

The cerebral function analysis monitor (CFAM) [see

Sebel PS, Maynard DE, Major E, Frank M, "The Cebrel Function Analysis Monitor (CFAM): A New Microprocessor-based Device for the On-line Analysis of the EEG and Evoked Potentials", BR J Anaesth 1983; 55: 1265-1270] is a commercially available system which provides a quantitative indication of anaesthestic depth. The CFAM system functions by analysing the spectrum of recorded EEG signals.

In an attempt to establish a more reliable method for measuring depth of anaesthesia, researchers have recently investigated the change in lower oesophageal contractility associated with anaesthesia. This contractility has been shown to be related to the end-tidal concentration of volatile anaesthetics. However, it has been found that this method is insufficiently discriminating at the interface between consciousness and unconsciousness to be used as a monitor of anaesthetic depth.

Despite the considerable amount of research carried out in this area, the anaesthesia indices obtained by researchers remain unreliable and there exists considerable reluctance to allow the widespread introduction of closed-loop anaesthesia control systems. WO 93/07804 describes a system in which a quantitative measure of anaesthetic depth is again obtained by analysing the frequency spectrum of the recorded signals. A system implementing this approach is the 'A1000'™ monitor available from Aspect Medical Systems, Inc. Massachusettes, USA.

It is an object of the present invention to overcome or at least mitigate certain of the disadvantages of the above systems and methods.

In particular, it is an object of the present invention to provide a system and method for generating a reliable quantitative measure of anaesthetic depth.

It is a further object of the present invention to provide an anaesthesia index which is a measure of anaesthetic depth and which may be used in a closed-loop anaesthesia control system.

According to a first aspect of the present invention there is provided a method of calculating an index indicative of anaesthetic depth, the method comprising subjecting a patient to a repetitive audio stimulus, monitoring auditory evoked potentials (AEP) produced by the patient, and providing a signal which is indicative of the coarseness of the monitored AEP signal as said index.

It has been found that the coarseness of the AEP signal provides a good indication of anaesthesia depth, with the coarseness of the signal being found to decrease as the depth of anaesthetic increases.

The term 'coarseness' is used here to means a combined measure of the amplitude and frequency of the monitored AEP signal i.e. a measure of the curvature of the signal. Typically, a high coarseness equates to a signal having large amplitude and high frequency whilst a low coarseness equates to a signal having low amplitude

and low frequency. Intermediate 'coarseness' may be a low amplitude/high frequency or a high amplitude/low frequency. It will be appreciated that it is difficult to give a precise definition of coarseness; coarseness is a relative measurement of a time varying signal which varies in amplitude and frequency. This term is used to define a parameter which can be readily used in the implementation of the method and apparatus.

In a preferred embodiment of the present invention, the monitored or raw AEP signal is divided into a series of sweeps or frames of a given duration, each sweep being synchronised with the repetitive audio stimulus. A number of sweeps n are recorded in sequence and are averaged to produce a time averaged sweep. For the time averaged sweep the anaesthesia index is calculated. Each time a new series of sweeps is recorded, a new time averaged sweep is determined from the most recent n sweeps and the anaesthesia index for that time averaged sweep calculated. In this way the anaesthesia index is constantly updated.

Where the method involves the use of a digital computer, the raw AEP signal is sampled at regular intervals to produce a digitised AEP signal. A preferred method of obtaining said indication of coarseness is to obtain a measure of the differences between neighbouring sample points. In the case where a moving time averaged sweep is obtained, this measure may be a function of the sum of the square roots of the difference between every

two adjacent sample points in the time averaged sweep.

According to a second aspect of the present invention there is provided a method of maintaining closed-loop control of an anaesthesia system, the method comprising supplying an anaesthetic to a patient, calculating an anaesthetic depth index according to the above first aspect of the present invention, and regulating the anaesthetic supply to maintain the anaesthesia depth index at or near a predetermined level.

According to a third aspect of the present invention there is provided a system for calculating an index of anaesthetic depth, the system comprising a signal generator for subjecting a patient to a repetitive audio stimulus, electroencephalographic (EEG) recording means for recording auditory evoked potentials (AEP) from the patient, and computer means for generating a signal indicative of the coarseness of the recorded AEP signal.

According to a fourth aspect of the present invention there is provided an anaesthesia control system comprising a system for calculating an index of anaesthetic depth according to the above third aspect of the present invention for a patient, and anaesthetic supply means including a regulator for regulating the supply of anaesthetic to the patient to maintain the anaesthetic depth index at a predetermined level.

The present invention is particularly applicable to anaesthesia systems which use a liquid anaesthetic, such as propofol, the dosage of which can be very accurately

regulated.

For a better understanding of the present invention and in order to show how the same may be carried into effect reference will now be made, by way of example, to the accompanying drawings in which:

Figure 1 shows schematically an anaesthesia control system embodying the present invention;

Figure 2 is a block diagram of an EEG amplifier of the system of Figure 1;

Figure 3 shows a detailed circuit diagram for an EEG amplifier of Figure 2;

Figure 4 illustrates the collection of 256 consecutive AEP frames using the system of Figure 1;

Figure 5 illustrates a moving time averaged frame obtained from the 256 consecutive frames of Figure 4;

Figure 6 shows the general organisation of software used to control a microprocessor of the system of Figure 1;

Figure 7 is a flow chart of a background task of the software of Figure 6; and

Figure 8 is a flow chart of a foreground task of the software Figure 6.

There is shown in Figure 1 an anaesthesia control system for safely maintaining a patient 1 in an unconscious state whilst the patient undergoes surgery. The patient 1 wears a pair of earphones 2 which are driven by a signal generator 3 to sound "clicks" of 1ms duration at a frequency of 6.9Hz to the patient's ears.

The amplitude level of the clicks is maintained at 70dB above normal hearing level. It is well known in the field of neurophysiology that such repetitive clicks sounded in the ears of a patient will produce distinctive potentials, known as auditory evoked potentials (AEP), in the electroencephalographic (EEG) response of the patient.

A liquid anaesthetic, for example propofol, is supplied intravenously to the patient through a tube 4 from a pump 5. The pump is of a known type (e.g. Ohmeda 9000™ syringe pump) which is controlled to accurately regulate the anaesthetic dose given to the patient. A controller 7 is arranged to process AEP signals for the purpose of generating an anaesthetic depth index for display on a controller display 7a. The anaesthetist uses the displayed index to control the pump 5.

The controller 7 receives an analogue input signal from an EEG amplifier 8 which is shown in greater detail in Figure 2. The EEG amplifier comprises at its input a medical grade preamplifier 9 the output of which is fed to a main amplifier 10. Power is supplied to the EEG amplifier components from a power supply 12. The main requirements of the EEG amplifier 8 are:

1) A very high common mode rejection ratio (CMRR), typically in excess of 110dB, even when the electrode impedances are not matched;

2) A frequency response in the range 1 to 300Hz;

3) The amplifier should be portable with small physical

dimensions;

4) The system should be suitable for theatre use, i.e. with shielded or guarded leads, appropriate patient isolation, immunity to diathermy and other sources of interference.

Figure 3 shows in greater detail the circuitry comprising the EEG amplifier 8. The preamplifier 9 is provided by an IA 297 medical grade isolation amplifier (Intronics, USA) which provides full patient protection from leakage currents and amplifier fault currents. This applies to both input protection and input/output isolation currents. The IA 297 is an ultra low noise true medical isolation amplifier which can operate at common mode input voltages of up to 5000V DC continuous. The common mode rejection ratio (CMRR) is 170dB with a balanced source impedance and 160dB with a 5KΩ source imbalance. The input noise voltage of the preamplifier is 0.3μV (10Hz to 1kHz rms) and the current noise is 4pA (0.05Hz to 1kHz rms). The input bias current is 200pA and is limited to 10μA in the event of failure of any component. The frequency response of the preamplifier is from DC to 10KHz and the overload recovery time is 20ms. The IA 297 provides an overall gain of x10.

The output from the preamplifier U1 is filtered by the high-pass filter network C1-R1 which provides a -3dB cut-off point at 0.9Hz. The filtered signal is then amplified by two identical amplification stages arranged in series. Each amplification stage is based around an

operational amplifier (OP77) which offers exceptional gain linearity with an equivalent input noise of 10nV/√Hz. The gain of each amplification stage is x94 to give an overall amplifier gain at the output of the second amplification stage of 88360 (10 x 94 x 94).

The output from the second amplification stage is supplied to a digital attenuator comprising a 12 bit digital-to-analogue converter IC3 which has a linearity error of 0.05% fullscale. This error is substantially independent of the voltage reference. The output from the attenuator is supplied to a wide bandwidth JFET operational amplifier IC4, which has an input bias current of 50pA and an equivalent input noise of 25nV/√Hz and which acts as a buffer amplifier having a gain of x1.

The output stage of the EEG amplifier 8 consists of a further x1 gain amplifier IC5 which allows a DC offset to be introduced to the amplified signal. This offset simplifies the connection to subsequent unipolar analogue to digital converters.

At intermediate points in the EEG amplifier, the signal is filtered by three low-pass first order filters (C2-R3, C3-R5 and C5-R9) which each have a -3dB cut-off point at 219Hz.

All of the resistors used in the EEG amplifier are precision metal film resistors with a 0.1% tolerance and a temperature coefficient of ± 15ppm/°C. The polarised capacitors of the amplifier are solid tantalum and the non-polarised capacitors are metallised polycarbonate

film with 5% tolerance and a temperature coefficient of ±50ppm/°C. Ceramic bypass capacitors are used to reduce instabilities caused by transients in the power supply lines.

The power supply unit for the EEG amplifier is of a conventional linear AC/DC design which provides high stability, low noise outputs of +15V, ±9V and +5V for the various stages of the amplifier. It also offers 5000V isolation between its primary and secondary coils. Power supplies having these characteristics are commercially available from, for example, 'RS', 'Amplicon', or 'Tandy' (all TM's).

The EEG amplifier 8 is situated as close as possible to the head of the patient and is coupled to three electrodes attached to the patient's head. A first electrode is placed on the right forehead (+), a second electrode is placed on the right mastoid (-), and the third electrode is placed on the middle of the forehead (reference). It has been found that standard disposable ECG electrodes (for example M-00-S by Medicotest) provide acceptable results provided that the patient's skin is carefully cleaned with alcohol swabs prior to attaching the electrodes with electrode jelly.

There are two very important reasons for ensuring that the electrode/skin impedances of the electrodes are as low as possible. Firstly, thermal or Johnson noise is generated by the electrode/skin resistance and is proportional to the square root of the resistance.

Secondly, the CMRR is reduced significantly if the electrodes have imbalanced impedances. The balancing of the impedances is easier to achieve if the impedances are as low as possible.

More recently, a new type of electrode, known as "Zipprep" TM (produced by Aspect Medical Systems), has become available. These electrodes achieve very low impedances with minimal skin preparation and are suitable for use with the system described herein.

With reference to Figure 1, the controller 7 is used to trigger the signal generator 3 to sound repeated clicks in the patient's right ear. Synchronisation of the signal generator is important in ensuring that the anaesthesia index, calculated as described hereinbelow, is as reliable as possible.

The physical construction of the microprocessor based controller 7 will not be set out in detail here as it is relatively standard. Indeed, whilst it may be preferable to design a purpose built controller in order to achieve a more portable and cost efficient design, the controller could be a standard desktop or notebook personal computer.

Before describing the structure of the control program, the method used to calculate an index of anaesthesia depth will be described.

In order to calculate the anaesthetic depth index, a recorded EEG signal is sampled at a rate of 1.7KHz. These samples are buffered in "sweeps" of 256 samples

such that each sweep extends over a duration of 144ms. As illustrated in Figure 4, a memory table of the controller 7 is created to store 256 consecutive sweeps. When a first group of 256 sweeps have been recorded, an averaged AEP curve or sweep is generated by averaging the 256 sweeps, i.e. by averaging the recorded 256 samples in each column of the memory table as illustrated in Figure 5.

Each time a new 256 sample sweep is recorded, the memory table shown in Figures 4 and 5 is updated by discarding the sweep at the top of the table i.e. sweep 1, and adding the new sweep to bottom of the table, i.e. as new sweep 256. A new time averaged sweep is then generated so that over a period of time a sequence of moving time averaged sweeps are created. This technique allows a faster response of the system to changes in the AEP signals.

A common source of error in AEP signals are artefacts which arise mainly from patient or electrode movement and the use of diathermy during surgery. Each newly recorded sweep is therefore examined to see if the signal amplitude at any point in the sweep exceeds a preset limit. If this limit is exceeded, the sweep is rejected and is not added to the table of Figure 4. Typically, several subsequent sweeps (for example seven) following a sweep detected as containing an artifact are rejected before sweeps are once again added to the table of Figures 4 and 5. In order to further enhance the time

averaged sweeps, these sweeps are filtered by a digital low-pass finite impulse response (FIR) filter. The frequency response of this filter is 0-0.049 of the Nyquist interval. The filter is a 35 point filter (18 coefficients) having a raised cosine window.

The FIR filter is described by the difference equation:

$$y(n) = \sum_{k=o}^{M-1} b_k x(n-k)$$

Where x(n) is the input to the filter, y(n) is the output, M is the number of coefficients (in this case 35), and b_k are the coefficients.

FIR filters have a number of advantages including their linear phase response and their high level of stability which results from the absence of feedback.

Once a moving time averaged and filtered frame has been obtained as described above, it is possible to calculate an index of anaesthesia depth. It has been observed that when patients lose consciousness, the amplitudes of most AEP peaks are reduced and their latencies are generally also increased. These changes occur almost simultaneously, and in the same direction, with all patients. A suitable index therefore is one which reflects these changes.

An empirical algorithm has been developed for calculating such an index and is based upon the sum of the square roots of the difference between every two successive points in the moving time averaged sweep.

This auditory evoked potential index is given by the following equation:

$$AEP = k \sum_{i=1}^{255} \sqrt{|x_i - X_{i+1}|}$$

Where x_1 to x_{256} are the sample points of the time averaged frame and k is a scaling constant equal to 0.25 x $\sqrt{V^{-1}}$.

The AEP index is calculated for every filtered time averaged sweep and a plot of the index against time can be generated by the controller 7 for display on the controller display 7a. When the patient is awake the index is typically in the range 80 to 90 whereas during anaesthesia it is typically in the range 35 to 40. When the patient recovers consciousness, the index usually returns to a value slightly lower than the value immediately prior to anaesthesia.

Figure 6 shows in general terms the organisation of the controller software which implements the algorithm described above for calculating the AEP index as a measure of anaesthetic depth. The program has a multi-tasking organisation with a foreground task and a background task running parallel to one another. These tasks are completely independent and communicate through "semaphores". The foreground task acts as an interface between the user and the background task causing the background task to initialise, start and stop.

Figure 7 shows in more detail the structure of the

background task. The recorded EEG signal is received by an analogue to digital converter of the controller (not shown) which, for sweeps consisting of 256 samples and with a duration of 144ms, generates hardware interrupts at a rate of 1.78KHz. These hardware interrupts cause the background task to read the data currently on the output of the ADC. In one cycle of the background task, from "start" to "end", a new single sample point is added to the memory table. If an artefact is detected as being present in a given sweep, that sweep is discarded. At the beginning of each new sweep, a further click is generated in order to ensure correct synchronisation of the subsequently generated sweep with the click. When the last point in each sweep is obtained, a new moving time averaged frame is calculated.

Figure 8 shows the general structure of the foreground task which interfaces the user to the background task. Once the foreground task is initialised, and has initialised and started the background task, it obtains the most recently generated time averaged sweep from the background task. This sweep is filtered using the FIR filter described above and the anaesthesia depth index calculated. The index is displayed on the controller display 7a to be viewed by the anaesthetist.

It will be appreciated by the skilled person that various modifications may be made to the above described embodiment without departing from the scope of the

invention. In particular the system may be made into a closed loop anaesthesia control system by providing a control output, corresponding to the determined anaesthetic depth index, from the controller 7 to the pump 5. Thus is indicated in Figure 1 by the dotted line 6.

FIG. 1

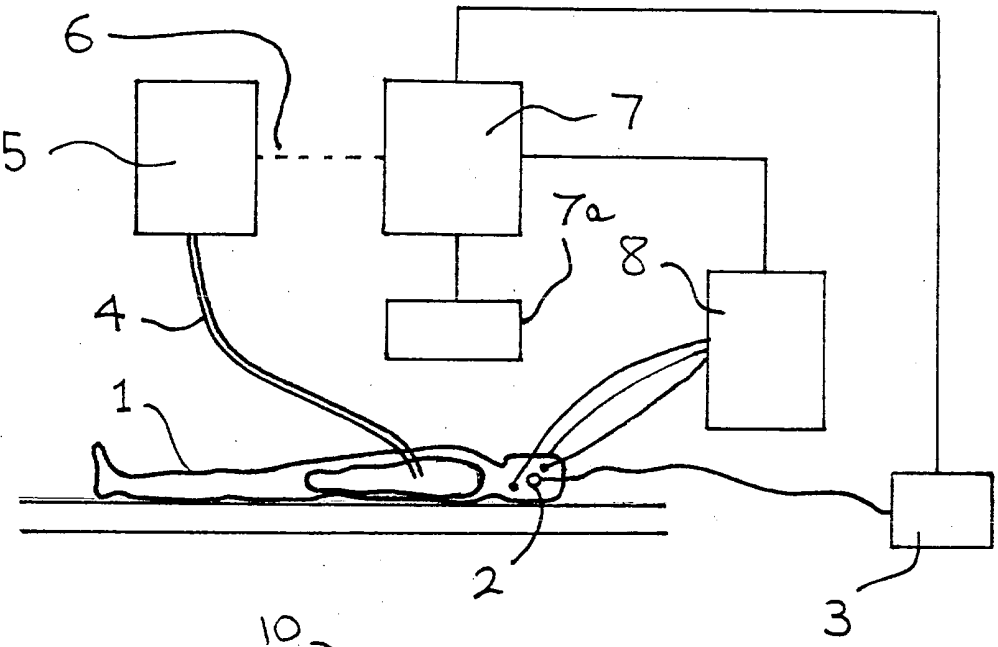
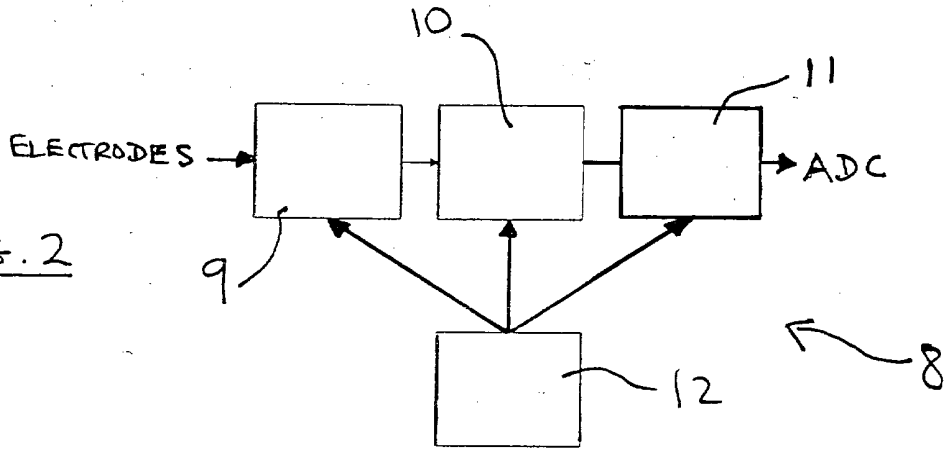


FIG. 2



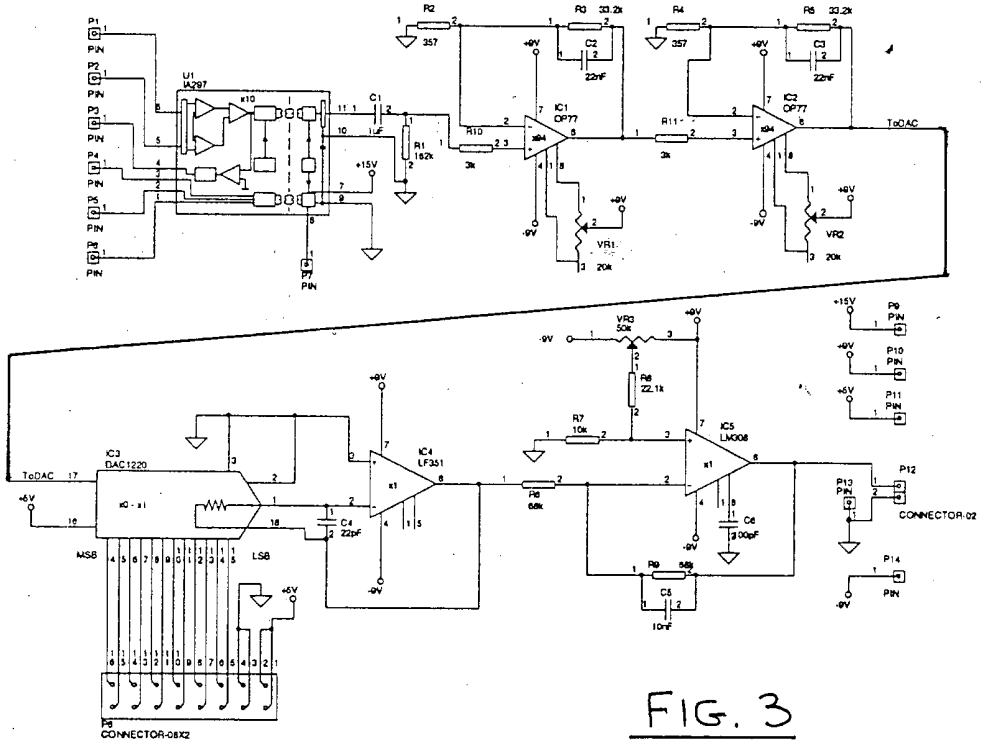


FIG. 3

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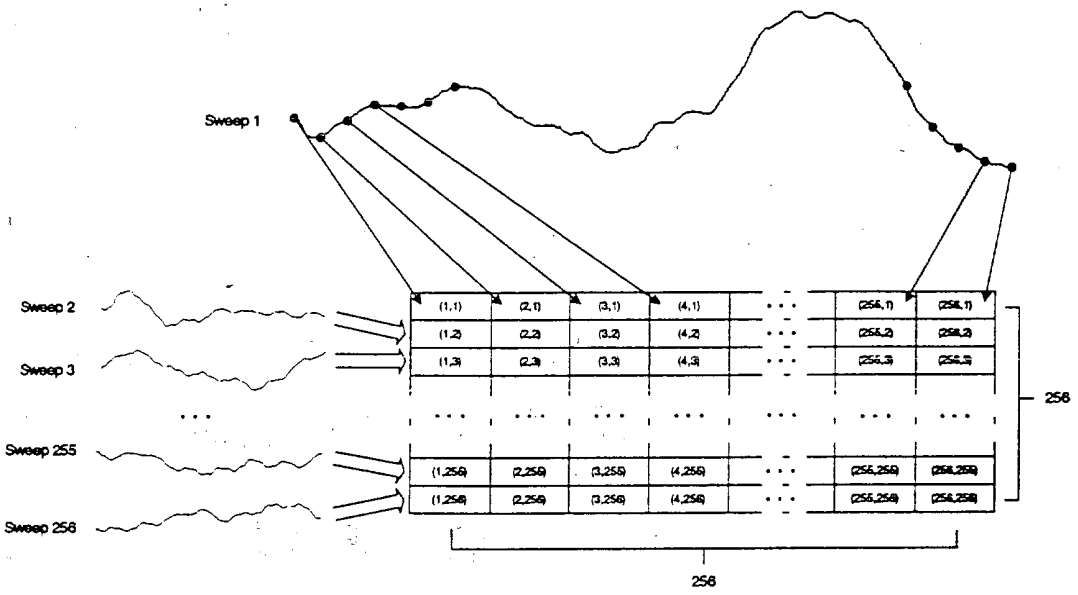

FIG. 4

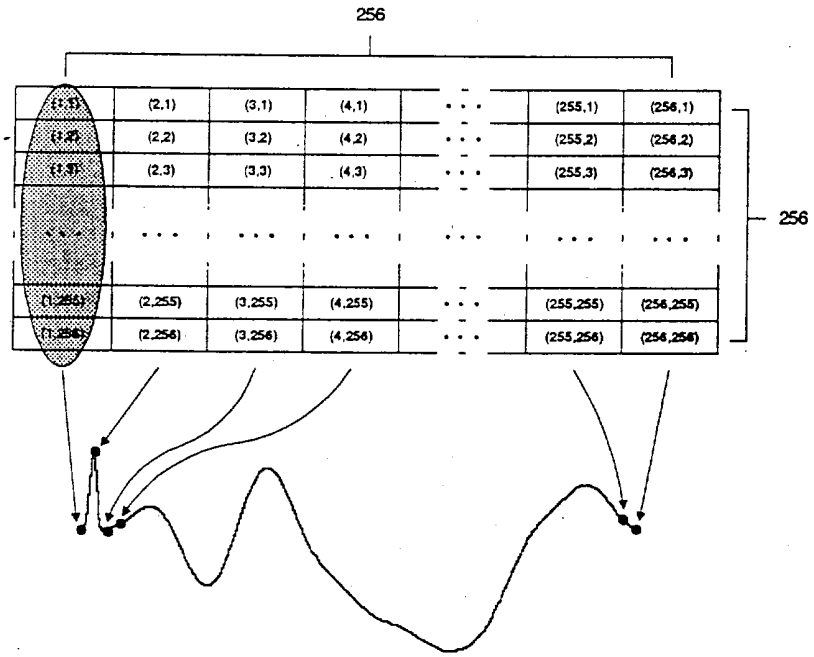

FIG. 5

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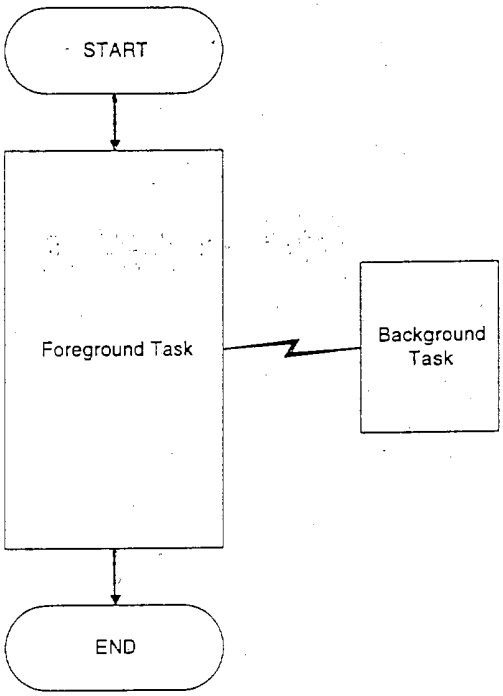

FIG. 6

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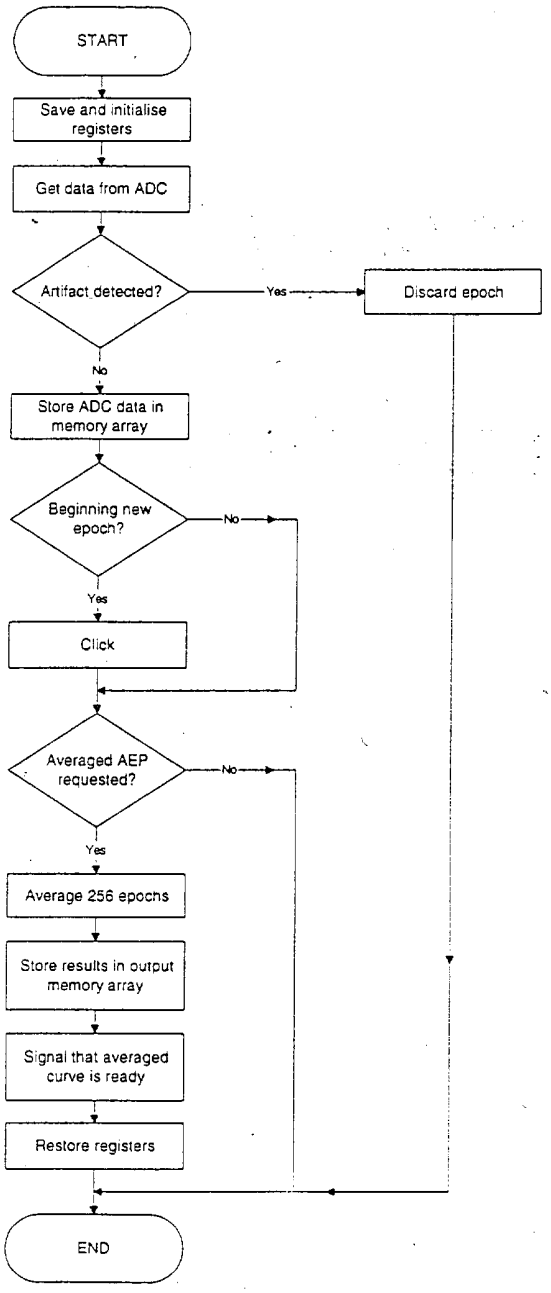
START
Save and initialise registers
Get data from ADC
Artifact detected?
Yes
Discard epoch
No
Store ADC data in memory array
Beginning new epoch?
No
Yes
Click
Averaged AEP requested?
No
Yes
Average 256 epochs
Store results in output memory array
Signal that averaged curve is ready
Restore registers
END

FIG. 7.

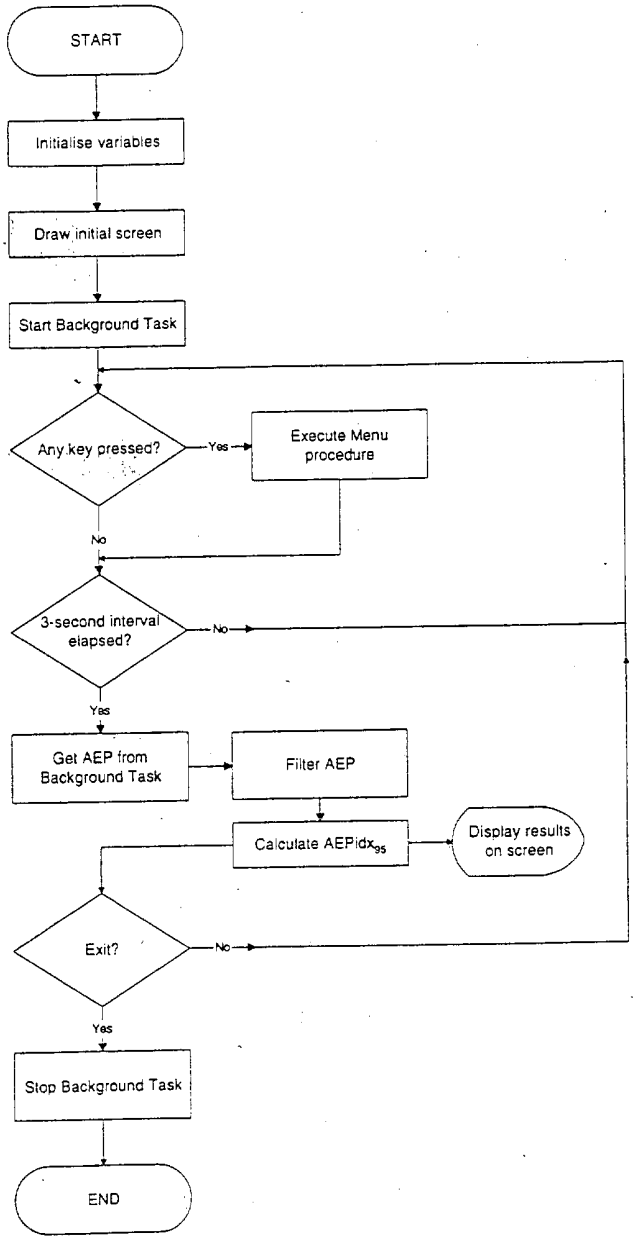
START
Initialise variables
Draw initial screen
Start Background Task
Any key pressed?
Yes
Execute Menu procedure
No
3-second interval elapsed?
No
Yes
Get AEP from Background Task
Filter AEP
Calculate AEPidx95
Display results on screen
Exit?
No
Yes
Stop Background Task
END

FIG. 8

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